REMARKS

Claims 1, 3, 5, 6, 8, 10, 12-14, 16, 40, and 41 are now pending in the application and were rejected. Claims 1, 8, 10, 12, 13, 14, 30, 40, 41 have been amended. Claims 2, 4, 7, 9, 11 and 15-39 have been cancelled. No new matter has been added by way of these amendments, and as discussed below, support for each amendment can be found in the original claims as filed and throughout the specification. Reconsideration of the pending claims is respectfully requested.

Application Status

Applicants would like to thank the Office for entry of the amendment mailed to the Patent and Trademark Office (PTO) on December 17, 2003. However, Applicants would like to clarify for the record that although claim 3 was labeled as "Currently amended" it should have been labeled "Previously presented" because no amendment was made.

Withdrawn Rejections

Applicants appreciate the rejection withdrawals discussed in paragraphs 5-8, 10 and 12-16.

Pending Issues

Applicants thank the Office for the thorough review of the last response and the summary of issues pending in the instant application, which are listed in paragraph 33 of the Office Action. Applicants address each of these issues in the order discussed in paragraph 33.

The Specification: (Paragraph 33: a-b)

The specification was objected to for allegedly lacking complete continuity data. Specifically, a claim of priority to PCT/US97/23014 filed December 12, 1997 was requested by the Office to be added to the first paragraph of the specification. The Office pointed out that the Application Data Sheet contains a claim of priority to PCT/US97/23014. Applicants have removed the claim of priority to PCT/US97/23014 filed December 12, 1997. Additionally, Applicants herein submits a revised Supplemental Application Data Sheet (SADS) removing the claim of priority to PCT/US97/23014. In view of this amendment and the SADS, the issue of priority has been addressed.

The Office also objected to the specification for failing to identify a sequence properly. Applicants thanks the Office for pointing out the inadvertent deletion in the Response mailed to the PTO on July 28, 2003, of the identifier "SEQ ID NO:7", on page 24, in the paragraph starting on line 17. Applicants have restored the identifier in the current amendment.

The Pending Claims are Definite: (Paragraph 33 c-j)

Claim 10 stands rejected under 35 U.S.C. § 112, second paragraph for allegedly being indefinite for reciting the phrase "expression system for a cell-based detection system . . . [for] a polyketide responsive target for a polyketide". The Office suggested amending the claim to read "an expression system for a cell-based detection system that comprises at least one nucleotide sequence that encodes a protein that is responsive to a polyketide." Applicants have amended claim 10 based on the Office's suggestion. Accordingly, Applicants asserts that the language of claim 10 is clear and meets the requirements of 35 U.S.C. § 112, second paragraph.

Claim 1, 3, 5, 6, 8, 10, 12-14, 16, 30-34, 37, and 39-41 stand rejected under 35 U.S.C. § 112, second paragraph, as being allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regards as the invention. Specifically, the Office rejected these claims because the abbreviations "KS" and "AT" were recited in claim 1 and not properly defined. Also, repeated abbreviation definitions appearing in claims 8, 12, 13, 30 and 37 were redundant. Claim 1 has been amended to define these abbreviations. Claims 8, 12, and 13 have been amended to remove the repeated definition and to recite only "PKS". Claims 30-34, 37, and 39 have been cancelled.

Claims 1, 3, 5, 6, 8, 10, 12-14, 16, and 40-41 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for reciting the phrase "comprising . . . an ACP activity." Claim 1 has been amended to clarify that the "ACP activity" refers to the transfer of a carbon unit from CoA to the conserved Ser residue of the ACP moiety. The Office states that in claims 1 and 8, the phrase "comprising ... an ACP activity" is unclear since both KS and AT domains are included as "catalytic regions". Applicants have amended claims 1 and 8 to read "an ACP domain". These amendments should be sufficient to provide consistency throughout the claims. The Office is invited to contact the undersigned if the Office would prefer another term to be recited in the claim.

The Office rejected claims 13-14 as allegedly being indefinite for reciting "different" PKSs. The Office stated that this term in claim 13 of "different" PKS is unclear. The specification makes clear that a number of different PKSs were known and could be employed by the presently claimed invention. For example, page 7, lines 9-20 of the specification describes the different PKSs that can be used in the host cells of the invention.

> "The invention herein employs expression systems for the catalytic activities involved in all of the aromatic, modular and fungal PKS systems. The proteins produced may contain the native amino acid sequences and thus the substrate specificities and activities of the native forms, or altered forms of these proteins may be used so long as the desired catalytic activity is maintained. The specificity and efficiency of this activity may, however, differ from that of the native forms. Certain activities present in the native system, however, can be intentionally deleted. Further, components of various aromatic systems can be mixed and matched, as well as can components of various modules of the module systems. PCT application WO 95/08548, referenced above and incorporated herein by reference describes the construction of hybrid aromatic PKS systems where, for example, open reading frames of actinorhodin are included in expression vectors with open reading frames from alternative aromatic systems." (Emphasis added).

Also, page 8, lines 21-29, describe how PKS activities from various sources can be used as well as their mutated forms.

> "The combinatorial possibilities for synthesis of aromatic PKS systems depend on the nature of the iteratively used sites and the presence or absence of the optional activities that are not part of the minimal PKS system required for the Claisen condensation which represents the synthetic mechanism for the end-product polyketide. Thus, while the aromatic PK synthase must contain a KS/AT, ACP and CLF, the other catalytic activities, *i.e.* KR, ARO, and CYC are optional. Fungal PK synthases require only KS, AT, and ACP functionalities, as do the modular PKS systems. Various combinations of these activities from various sources can be used as well as their mutated forms." (Emphasis added).

In addition, on page 9, lines 15-26, it is stated how mutated or modified forms of PKSs can be employed.

> "In addition to controlling the number of modules, the modules can be genetically modified, for example, by the deletion of a ketoreductase domain as described by

> Donadio, S. *et al. Science* (1991) 252:675-679; Donadio, S. *et al. Gene* (1992) 115:97-103. In addition, the mutation of an enoyl reductase domain was reported by Donadio, S. *et al. Proc Natl Acad Sci USA* (1993) 90:7119-7123. These modifications also resulted in modified PKS and thus modified polyketides.
>
> As stated above, in the present invention, the coding sequences for catalytic activities derived from the aromatic, fungal or modular PKS systems found in nature can be used in their native forms or modified by standard mutagenesis techniques to delete or diminish activity or to introduce an activity into a module in which it was not originally present. For example, a KR activity an be introduced into a module normally lacking that function." (Emphasis added).

Accordingly, Applicants assert that the meaning of the phrase "wherein said first and second PKS are different" in claim 13 is clearly defined by the specification and that the language of claims 13-14 is clear and meets the requirements of 35 U.S.C. § 112, second paragraph.

Claims 14, 16, 30-31, 37, and 39-41 stand rejected as allegedly being indefinite for reciting "encoding a ketoreductase (KR) activity" and other similar phrases that were unclear to the Office. Applicants have amended claim 14 to include the phrases "a protein having ketoreductase (KR) activity", "a protein having KR activity and a protein having dehydratase (DH) activity", "a protein having KR activity, a protein having DH activity and a protein having enoylreductase (ER) activity", and "a protein having thioesterase (TE) activity". Accordingly, Applicants asserts that the language of claims 14, 16, and 40-41 is clear and meets the requirements of 35 U.S.C. § 112, second paragraph. Claims 30, 31, 37, and 39 have been cancelled.

Claims 32, 37, and 39-41 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for reciting the phrase "expression system for a holo ACP synthase gene". Claims 32, 37, and 39 have been cancelled. Claims 40 and 41 have been amended to remove any dependency from cancelled claims 32 or 37 and now only depend on claim 1 or 16. Claims 1 and 16 both recite genes for an ACP synthase that pantetheinylates said PKS and said ACP synthase is not associated with fatty acid synthesis. Applicants assert that this definition is suitably clear. Accordingly, the language of claims 40 and 41 is definite and particular.

Claims 33 and 34 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for reciting the phrase "produce a polyketide synthase activity". Claims 33 and 34 have been cancelled. Thus, this rejection is moot.

Claim 40 stands rejected under 35 U.S.C. § 112, second paragraph, as being allegedly indefinite. The Office states that the phrase "derived from *Bacillus*" is unclear as to its meaning. Applicants have, based on Office's suggested terminology, amended claim 40 to recite "native to *Bacillus*". Accordingly, Applicants asserts that the language of claim 40 is clear and meets the requirements of 35 U.S.C. § 112, second paragraph.

The Pending Claims are Fully Supported by the Present Disclosure: (Paragraph 33: k-m)

Claims 1, 3, 5, 6, 16, 32, 34, 37, 39, and 40 stand rejected under 35 U.S.C. § 112, first paragraph. Specifically, the Office alleged that "[t]he instant rejection concerns the lack of written description for host cells or vectors containing expression systems for holo ACP synthases that pantetheinylate a PKS."

The present indefiniteness rejection turned on two points, the first, that the pending claim allegedly read on an inoperative embodiment. The second point was that, according to the Office, one of ordinary skill in the art would not know how to differentiate between a fatty acid synthesis-associated ACP and a PKS-associated ACP. Applicants submit that one of ordinary skill in the art would have found the subject matter of the pending claims to be definite in light of the available art and the teachings provided in the specification.

Applicants note that claim 1 was amended in the response submitted on December 17, 2003 to read, "wherein the ACP synthase pantetheinylates said PKS and said ACP synthase is not associated with fatty acid synthesis...." Thus, ACP synthases such as *E. coli* fatty acid synthase holo-ACPS (ACPS) as described at page 21, line 7, is not covered by claim 1. ACPS, as pointed out by the Office, and as described in the specification at page 21, lines 27-28, was unable to activate the DEBS fragment. Thus, the language of the claims is sufficient to exclude the inoperative embodiment of the *E. coli* ACP, which is associated with fatty acid synthase activity.

As discussed in the response submitted December 17, 2003, the specification teaches what type of ACP synthases should be used in the claimed system. Specifically, synthases associated with polyketide synthesis or with synthesis of nonribosomal proteins are to be used with the claimed subject matter. In addition, the state of the art at the relevant time period was replete with examples of effective ACP synthases as defined by the specification. Specifically, the art was aware of particular a number of holo-ACP synthases that were classified as being associated with either polyketide synthesis (PKS) or fatty acid synthesis (FAS).

Lambalot *et al.* were some of the first workers in the field to characterize the phosphopantetheinyl transferase superfamily. In their 1996 Chemistry & Biology paper, Lambalot *et al.* discuss three *E. coli* ACP synthases, ACPS, EntD and o195. (Lambalot, *et al.*, Chem Biol. 1996 Nov;3(11):923-36.) ACPS and EntD are specific for fatty acid synthase and enterobactin synthetase. The *B. subtilis* Sfp is specific for surfactin synthetase.

Table 1 of the Lambalot *et al.* paper provides a list of ACP synthase homologs, the sequences of all but two of which were publicly available at the relevant time period. This list clearly delineates ACP synthases associated with fatty acid synthesis and those associated with polyketide synthesis. Interestingly, the ACP synthases that are approximately 225 amino acids in length are primarily associated with polyketide synthesis while those ACP synthases, such as *E. coli* ACPS, associated with fatty acid synthesis are either markedly shorter in length (*E. coli* ACPS 126 amino acids) or significantly longer, such as FAS2 of *S. cerevisiae*, which is 1894 amino acids long. The model holds when one looks at HI0152 of H. influenzae, which was classified as associated with fatty acids by Lambalot, *et al.*, but which has since been reclassified as being in the polyketide associated class comprising sfp, *Bacillus subtilis* gsp, hetI, and acpT. (See Accession No. P43954 for HI0152.)

In view of the structural similarities shared by those ACP synthases, namely their overall amino acid length (approximately 225 amino acids), one of ordinary skill in the art could readily select ACP synthases that are associated with polyketide synthesis as opposed to those that are associated with fatty acid synthesis. Furthermore, the structural differences observed between ACP synthases associated with fatty acid synthesis and those associated with polyketide synthesis

provides a concrete selection criterion that one of ordinary skill in the art could use with the disclosed assays, to select appropriate synthases for use with the claimed invention.

Thus, the present specification contains sufficient written description to support the pending claim limitation selecting PKS associated ACP synthases. Accordingly, in view of the language of the pending claims, the support for the claim language found in the specification and the state of the art at the relevant time period, one of ordinary skill in the art would reasonably conclude that Applicants were in possession of the claimed subject matter at the time the application was filed.

Claims 1, 3, 5, 6, 16, 32, 34, 37, 39 and 40 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly reciting subject matter not supported by an enabling disclosure. Specifically, the Office has alleged that the pending claims are not enabled for all holo ACP synthases that pantetheinylate PKSs. Applicants note that the scope of the pending claims does not encompass all holo ACP synthases that pantetheinylate PKSs. Rather, the pending claims encompass the use of those holo ACP synthases that are associated with PKS as opposed to those associated with fatty acid synthesis. In view of the discussion above, Applicants submit that one of ordinary skill in the art would be able to practice the full scope of the claimed invention without undue experimentation. As such, the subject matter of the pending claims is properly enabled.

Claims 8, 10, and 12-14 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter not supported by an enabling disclosure. Specifically, the Office asserts that the instant specification teaches that non-PKS, prokaryotic host cells require an additional factor, a phosphopantetheinyl transferase, such as *sfp*, as well as recombinantly expressed PKS genes to produce polyketides. The Office also states that the instant specification provides no guidance or working examples of making polyketides in *E. coli*, for example, without these additions. Although Applicants do not agree with the Office's latter statement, solely to expedite prosecution, Applicants has amended claim 8 to include the phrase "a recombinant expression system for a holo ACP synthase capable of being expressed and effective in the pantetheinylation of said PKS". Accordingly, claim 16 has been cancelled. These amendments are sufficient to supply the element allegedly missing from the pending claims. As such, the pending claims are fully supported by an enabling disclosure.

The Pending Claims are Novel Over U.S. Patent No. 6,579,695 (Paragraph 33: n)

Claims 1, 30-34, 37, 39 and 40-41 stand rejected under 35. U.S.C. § 102(e) as allegedly being anticipated by U.S. Patent No. 6,579,695 (hereinafter "the '695 patent"). To be anticipatory, a reference must teach each and every limitation of the claimed invention. The '695 patent does not teach using a host cell which, in an unmodified form, does not produce polyketides. As such, the pending claims are not anticipated by the teachings of the '695 patent.

The Pending Claims are Nonobvious (Paragraph 33: o-p)

Claim 5 stands rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable the '695 patent. To constitute a *prima facie* case of obviousness, the cited art must, *inter alia*, teach or suggest all the limitations of the claimed invention. As discussed above, the '695 patent does not teach or suggest the use of an *E. coli* or yeast host cell which, in an unmodified form, does not produce polyketides. Because the cited art files to teach or suggest all the limitations of the claimed invention, the Office has failed to articulate a prima facie case of obviousness. Accordingly, the subject matter of claim 5 is patentable over the teachings of the '695 patent.

Claims 8, 12-14, 16, and 40-41 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over the '695 patent in view of Khosla's U.S. Patent No. 5,712,146 (hereinafter "the '146 patent"). Neither the '695 patent nor the '146 patent teach or suggest the use of *E. coli* or yeast host cells which, in an unmodified form, do not produce polyketides. The teachings of the '695 patent are discussed above. The '146 patent discusses the use of prokaryotes generally and discusses the use of *Streptomyces coelicolor* cells as host cells as preferred embodiments. However, the '146 patent does not teach or suggest the use of host cells which, in an unmodified form, do not produce polyketides. Furthermore, *S. coelicolor* are neither *E. coli* nor yeast and unmodified *S. coelicolor* cells are known to produce polyketides.

In conclusion, because the proposed combination of the '695 and '146 patents do not teach or suggest all the limitations of the claimed invention, the pending claims are nonobvious over these references.

Double Patenting: (Paragraph 33: q-s)

The Office rejected claim 3 under 35 U.S.C. §101 as allegedly claiming the same invention as that of claim 3 of U.S. Patent No. 6,033,883 (hereinafter "the '883 patent"). "Same invention" means identical subject matter. *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1984). Specifically, the Office alleged that both claims are drawn to *E. coli* or yeast host cells having expression systems for a PKS (6-MSAS) and a holo ACP synthase. The claims at issue read on different subject matter. For example, the presently pending independent claim 1 recites a modified recombinant E. coli or yeast host cell which, in unmodified form, does not produce polyketides. No such limitation appears in claims 1, 2 or 3 of the '883 patent. As such, the subject matter of the respective claim 3s is sufficiently different so not to support a statutory double patenting rejection. Accordingly, Applicants request that the present rejection be withdrawn.

In addition, claims 1, 5, 6, 8, 10, 12-14, 16, 30-34, 37, 39, and 40-41 and claims 1, 3, 5, 6, 30-34, 37, and 39 stand rejected under the judicially created doctrine of obviousness-type double patenting over the claims of U.S. Patent Nos. 6,033,883 and 6,258,556, respectively. The instant application is a divisional of U.S. Patent No. 6,258,566, which is a continuation of U.S. Patent No. 6,033,883, and all three are commonly owned by Kosan Biosciences. Accordingly, two Terminal Disclaimers are proper to overcome the obviousness-type double patenting rejections, and are enclosed with the Response. Applicants do not necessarily agree with the non-statutory double patenting rejection but in an effort to expedite prosecution herein submits the two Terminal Disclaimers. Applicants assert that these two Terminal Disclaimers render both rejections listed above moot.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Office is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Office is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, Applicants petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no. 300622001610. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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Respectfully submitted,

By _____

James J. Mullen III, Ph.D.
Registration No.: 44,957
MORRISON & FOERSTER LLP
3811 Valley Centre Drive, Suite 500
San Diego, California 92130
(858) 720-7940